

LNG-IUS versus oral progestogen treatment for endometrial hyperplasia: a long-term comparative cohort study

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STUDY QUESTION: What are the regression and hysterectomy rates for women treated with the levonorgestrel-releasing intrauterine system (LNG-IUS) compared with oral progestogens for endometrial hyperplasia (EH)?

SUMMARY ANSWER: The LNG-IUS achieves higher regression and lower hysterectomy rates than oral progestogens in the treatment of complex and atypical hyperplasia.

WHAT IS KNOWN ALREADY: The LNG-IUS and oral progestogens are both equally used to treat women with EH. There is uncertainty about whether the LNG-IUS is a better therapy for EH.

STUDY DESIGN, SIZE, DURATION: This comparative cohort study included 344 women recruited from August 1998 until December 2010.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women with complex non-atypical or atypical EH were treated with the LNG-IUS ($n = 250$) or oral progestogens ($n = 94$) in a tertiary referral hospital. We evaluated the proportion of women who regressed or underwent hysterectomy after treatment with the LNG-IUS compared with oral progestogens by logistic regression adjusting for confounding. The time from diagnosis to regression was explored through a survival analysis.

MAIN RESULTS AND THE ROLE OF CHANCE: The follow-up rate was 95.3%. The mean length of follow-up in the two groups was $66.9 \pm \text{SD } 35.1$ months for the LNG-IUS and $87.2 \pm \text{SD } 45.5$ months for the oral progestogen group. Regression of hyperplasia was achieved in 94.8% (237/250) of patients with the LNG-IUS compared with 84.0% (79/94) of patients treated with oral progestogens (adjusted odds ratio (OR) = 3.04, 95% CI 1.36–6.79, $P = 0.001$). Hysterectomy rates were lower in the LNG-IUS group during follow-up (22.1, 55/250 versus 37.2%, 35/94, adjusted OR = 0.48, 95% CI 0.28–0.81, $P < 0.004$). Endometrial cancer was diagnosed in 8 (33%) women who had hysterectomy because of a failure to regress to normal histology during follow-up ($n = 24$).

LIMITATIONS, REASONS FOR CAUTION: The observational design cannot exclude residual confounding from unmeasured variables.

WIDER IMPLICATIONS OF THE FINDINGS: In treating EH, LNG-IUS achieves higher regression rates and lower hysterectomy rates than oral progestogens and should be the first-line therapy. Failure to achieve regression carries a high risk of underlying endometrial cancer and hysterectomy is advised.

Key words: endometrial hyperplasia / LNG-IUS / oral progestogens / prospective cohort study

Introduction

Endometrial hyperplasia (EH) is the precursor of endometrial carcinoma, which is the most common gynecological malignancy in the western world (Bray *et al.*, 2005). In 2007 in England and Wales, 7536 new cases of endometrial cancer were registered and, although, the incidence

of endometrial cancer is high, EH has an incidence of EH, which is three times higher, and can progress to cancer if left untreated (Reed *et al.*, 2009; Office for National Statistics, 2010). Without intervention, the risk of progression to carcinoma is $< 1\%$ for women with simple hyperplasia (SH), 3% for non-atypical complex hyperplasia (CH) and up to 29% for women with atypical complex hyperplasia (ACH) (Kurman *et al.*,

1985). ACH has also been associated with up to a 43% rate of concomitant carcinoma in women undergoing hysterectomy (Trimble *et al.*, 2006). As the rate of progression to carcinoma for SH is low and it often regresses spontaneously, treatment interventions are aimed at mostly CH and ACH patients.

The treatment modality selected is dependent upon the woman's desire to retain fertility, medical fitness for surgical intervention and histological diagnosis. In women in whom histological atypia is present, the recommended and undisputed definitive treatment remains hysterectomy. Traditionally, hysterectomy has been recommended for CH cases but it may not be the best option given the potential risks, especially for older or obese patients and those with significant co-morbidities. Medical management of EH is therefore advocated in such cases (Clark *et al.*, 2006). In a national survey, we found that >85% of gynecologists treat CH with the levonorgestrel-releasing intrauterine system (LNG-IUS) or oral progestogens (Gallos *et al.*, 2011). Oral progestogens have been used in various dosages and regimens to treat hyperplasia since 1959, with the most common treatment duration of 6 months and then stopping treatment after regression is confirmed (Kistner, 1959; Gallos *et al.*, 2011). However, a meta-analysis of observational studies found oral treatment to be inferior to the LNG-IUS in treating EH (Gallos *et al.*, 2010). This meta-analysis also highlighted the scarcity of high-quality comparative studies with long-term follow-up for assessing the efficacy of these two treatment options and called for further evidence to help decide which one is the treatment of choice (Gallos *et al.*, 2010). Our objective has been to conduct a large comparative cohort study with a long-term follow-up comparing the regression and hysterectomy rates of treatment with the LNG-IUS and with oral progestogens in patients diagnosed with CH or ACH.

Materials and Methods

This was a comparative observational study. Our cohort has been described before (Gallos *et al.*, 2013a,b,c) and briefly we recruited all women diagnosed with CH or ACH and who underwent treatment with the LNG-IUS or oral progestogens in a tertiary referral Hospital in Birmingham, UK. Women were reviewed in our gynecology outpatient clinic following diagnosis and were offered the LNG-IUS (Mirena®; Bayer Schering Pharma AG, Berlin, Germany), oral progestogens (3–6 months) or hysterectomy as part of our routine clinical practice. Women diagnosed with ACH were counseled and offered a hysterectomy. Women who declined surgery or who were medically unfit to undergo surgery were offered either the LNG-IUS or oral progestogens. This practice has remained unchanged since the onset of recruitment, along with follow-up endometrial biopsies to ensure regression 6 monthly for the first 2 years and yearly thereafter for up to 7 years. Recruitment for women treated with the LNG-IUS was prospective and started from August 1998 until December 2010. For women treated with oral progestogens, prospective recruitment started in August 2008. Women with CH and ACH treated with oral progestogens from August 1998 until August 2008 were invited for long-term follow-up in our clinic and have continued to be followed up ever since. Ethical approval from the Coventry and Warwickshire Research and Ethics Committee was obtained for this study (LREC 09/H1211/30) to collect and analyze linked data.

The primary outcome for this study was to determine the proportion of women with CH or ACH showing histological regression after treatment with the LNG-IUS compared with treatment with oral progestogens. For this assessment, the results of follow-up histological examinations were classified as: (i) complete regression—atrophy of glands, edematous fibrotic stroma or pseudodecidualization, with no evidence of hyperplasia or (ii)

persistence or progression—failure to completely regress with evidence of CH, ACH or carcinoma. The secondary outcomes we studied were the hysterectomy rate for each treatment, the time interval from treatment initiation to complete regression and the proportion of patients in both groups diagnosed with endometrial cancer during follow-up. All outcomes were evaluated with an intention-to-treat basis.

The baseline characteristics and outcomes for the LNG-IUS and oral progestogen groups were analyzed using Mann–Whitney *U*-tests for non-parametric data and Pearson χ^2 tests for categorical data. Analysis of outcomes between the treatment groups was performed by logistic regression to compute odds ratios with their 95% confidence intervals (CIs) adjusting for potential confounding factors. We adjusted for correlated confounding factors ($P < 0.1$) with both treatment modality and outcome and these were incorporated into the final model (Hosmer, 2000). We constructed our survival analysis using the Cox proportional hazards model as it accounts for variable duration of follow-up, censoring of subjects, proportionality of event occurrence and time-to-event (Lin and Wei, 1989). To convert the results of the Cox model into absolute risk estimates, we calculated survival within our population by using Kaplan–Meier estimates (Cox, 1972; Klein and Moeschberger, 2003). Missing data were handled by complete case analysis for our exposure (treatment modality) and outcomes (regression and hysterectomy) and by multiple imputation for confounding variables (Rubin, 1972; Schafer, 1997). All analyses were performed using STATA Version 12.1 (Stata Corp, College station, TX, USA).

Results

Of the 655 women diagnosed with CH or ACH over the 12-year study period, 361 women were treated with progestogens (Fig. 1). We had incomplete data on follow-up for 17 women and these were excluded. Our follow-up rate was therefore 95.3% (344/361). The final study group consisted of 250 women in the LNG-IUS group and 94 women in the oral progestogen group. The mean length of follow-up in the two groups was $66.9 \pm \text{SD } 35.1$ (range 12–148.2) months for the LNG-IUS and $87.2 \pm \text{SD } 45.5$ (range 13.2–162) for the oral

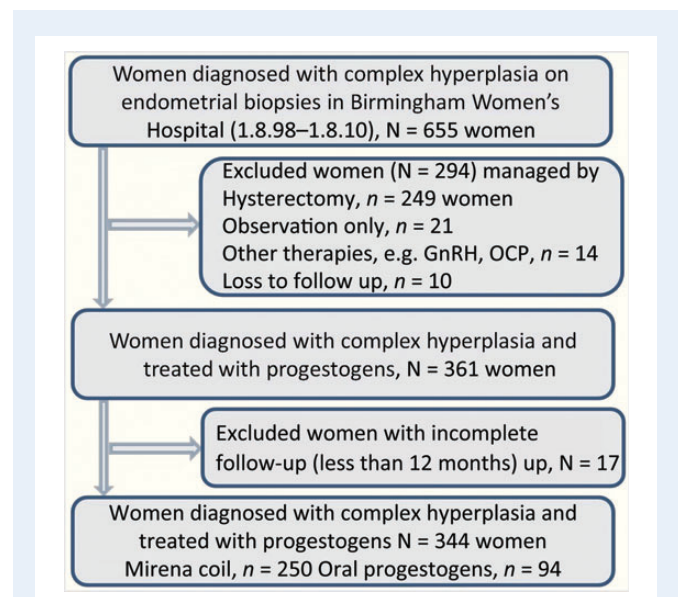


Figure 1 Schematic representation of patients included in study analysis.

progestogen group. The duration of treatment with oral progestogens consisted of 3 (29.8%, 28/94), 6 (63.8%, 60/94) or 12 months (6.4%, 6/94) and then the treatment was stopped. The most common type of progestogen therapy given was norethisterone (50%), followed by medroxyprogesterone acetate (43%), dydrogesterone (2%), megestrol acetate (1%) and a combination of therapies (4%). Progestogen therapy was given either cyclically (32%) or continuously (68%). Baseline characteristics between both treatment groups were compared and found to be similar for all variables with the exception of age and menopause (Table I). The women in the LNG-IUS group were older (mean 52.7 years \pm SD 10.6 versus 48.5 \pm 11.6, $P = 0.001$) and more often menopausal (52.4%, 131/250 versus 33%, 31/94, $P = < 0.001$) compared with the oral progestogen group. The body mass index was not available for 27/344 (7.8%) patients and also the endometrial thickness was not measurable in 9/162 (5.6%) of post-menopausal women.

Regression of hyperplasia was achieved in 94.8% (237/250) of patients with the LNG-IUS compared with 84% (79/94) of patients treated with oral progestogens (Table II) and this difference was found to be statistically significant (OR = 3.46, 95% CI 1.58–7.19, $P = 0.001$). Regression rates were significantly higher with LNG-IUS treatment than with oral progestogen treatment for CH (OR = 3.03, 95% CI 1.1–8.35, $P = 0.032$), but not for ACH (OR = 3.73, 95% CI 0.85–16.44, $P = 0.082$). Regression rates were also higher for CH compared with ACH for both the LNG-IUS (96.5, 221/229 versus 76.2%, 16/21; $P = < 0.001$) and oral progestogen groups (90.1, 73/81 versus 46.2%, 6/13; $P = < 0.001$). Hysterectomy rates were also

significantly lower in the LNG-IUS group compared with the oral group during follow-up (22.1, 55/250 versus 37.2%, 35/94, OR = 0.48, 95% CI 0.29–0.8, $P < 0.004$). From the total of 10 women (4 CH, 6 ACH) diagnosed with cancer during follow-up, 6 were originally treated with the LNG-IUS (6/250, 2.4%) and 4 were treated with oral progestogens (4/94, 4.3%; $P = 0.361$). They were all found to be at early stage endometrial cancer (Stage Ia, G1 for five women and Ib G1 for four women) apart from one woman who was diagnosed with endometrioid cancer of the ovary (Stage Ib). The 28 women who did not achieve regression were strongly advised to undergo hysterectomy; 24 eventually underwent this procedure in a median time of 12.9 months from diagnosis (IQR 10.1–16.4 months) and 8 were diagnosed with endometrial cancer on the hysterectomy specimens (33.3%, 8/24). Of the remaining four women, one is well and undergoing assisted reproduction treatment, two declined further biopsies and are currently undergoing long-term clinical follow-up only and one was lost to follow-up after 18 months. On logistic regression, age was found to be independently correlated with both treatment modality and the regression outcome. As this was a potential confounder, we adjusted the OR for the outcomes of EH regression and hysterectomy (Table II).

The survival analysis indicates that regression (Fig. 2) was higher with the LNG-IUS at 12, 18 and 24 months of follow-up (hazard ratio 1.48, 95% CI 1.14–1.92, $P = 0.002$). After 12 months of follow-up, the probability of regression fell to 57.4% (39/68) with the LNG-IUS and 38.9% (14/36) with oral progestogens, but the proportions diagnosed with cancer were 4.4% (3/68) with the LNG-IUS and 11.1% (4/36) with

Table I Baseline characteristics.

	LNG-IUS (n = 250) n (%)	Oral progestogens (n = 94) n (%)	P value
Age (years)	Mean 52.7 \pm SD 10.6	Mean 48.5 \pm SD 11.6	0.001
Parity	Mean 2.1 \pm SD 1.5	Mean 1.7 \pm SD 1.9	0.095
BMI (kg/m ²)	Mean 33 \pm SD 9.5	Mean 32.2 \pm SD 8	0.493
Endometrial thickness on USS (mm) for menopausal women	Mean 9.9 \pm SD 5.6	Mean 10.9 \pm SD 6.4	0.245
Ethnic group			
Caucasian	196 (78.4)	72 (76.6)	0.78
Asian	29 (11.6)	11 (11.7)	
Other	10 (4)	9 (9.6)	
Unknown	15 (6)	2 (2.1)	
Menopausal status			
Premenopausal	119 (47.6)	63 (67.0)	0.001
Post-menopausal	131 (52.4)	31 (33.0)	
Hypertensive	91 (36.4)	26 (27.7)	
Diabetic	41 (16.4)	13 (13.8)	
HRT/tamoxifen use in last 5 years			
None	199 (79.6)	81 (86.2)	0.165
HRT	42 (16.8)	10 (10.6)	
Tamoxifen	9 (3.6)	3 (3.2)	
Endometrial Histology			
Atypical hyperplasia	21 (8.4)	13 (13.8)	0.137
CH	229 (91.6)	81 (86.2)	

CH, complex hyperplasia.

Table II Outcomes of patients treated with LNG-IUS compared oral progestogens.

	LNG-IUS (n = 250) n (%)	Oral Progestogens (n = 94) n (%)	P value	OR	Adjusted OR
Time from diagnosis to last histological follow-up (months)	Mean 66.9 ± SD 35.1	Mean 87.2 ± SD 45.5	<0.001		
Regression of hyperplasia	237/250 (94.8)	79/94 (84.0)	0.001	3.46 (1.58–7.59)	3.04 (1.36–6.79)
CH	221/229 (96.5)	73/81 (90.1)	0.032	3.03 (1.1–8.35)	2.85 (1.04–7.98)
Atypical hyperplasia	16/21 (76.2)	6/13 (46.2)	0.082	3.73 (0.85–16.44)	2.89 (0.61–14.32)
Hysterectomy performed	55/250 (22.1)	35/94 (37.2)	0.004	0.48 (0.29–0.80)	0.48 (0.28–0.81)
Cancer diagnosed	6/250 (2.4)	4/94 (4.3)	0.361	0.55 (0.15–2.01)	0.53 (0.14–1.95)

CH, complex hyperplasia.

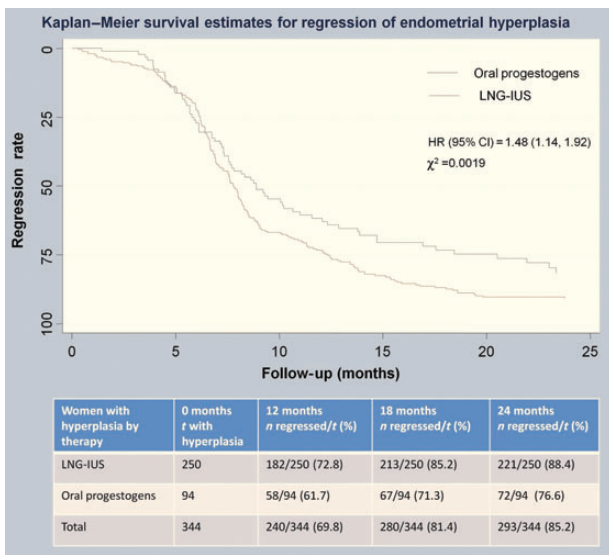


Figure 2 Kaplan–Meier survival curves for all events of EH regression in women treated either with the LNG-IUS or oral progestogens. CI, confidence interval; HR, hazard ratio; EH, endometrial hyperplasia.

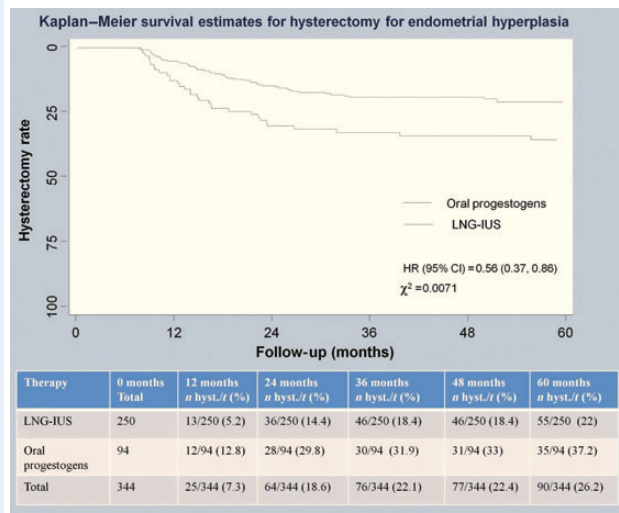


Figure 3 Kaplan–Meier survival curves for all events of hysterectomy for EH in women treated either with the LNG-IUS or oral progestogens. CI, confidence interval; HR, hazard ratio; hyst. = hysterectomy; EH, endometrial hyperplasia.

oral progestogens. The majority of the women achieved regression by 24 months and specifically it was achieved in 93.2% (221/237) of women who achieved regression by treatment with the LNG-IUS and 91.1% (72/79) of women who achieved regression by treatment with oral progestogens by this time point. The survival analysis for hysterectomy (Fig. 3) indicates that hysterectomy was less likely to happen in women treated with the LNG-IUS from 12 up to 60 months of follow-up (hazard ratio 0.56, 95% CI 0.37–0.86, $P = 0.007$). Specifically, by 60 months, 22.0% of women (55/250) treated with the LNG-IUS and 37.2% of women (35/94) treated with oral progestogens underwent hysterectomy.

Discussion

To our knowledge, this is the largest study with the longest follow-up period examining the efficacy of the LNG-IUS in the treatment of EH

and comparing it with the current standard treatment of oral progestogens. This study finds that complete regression of EH occurs more often in women treated with the LNG-IUS compared with women treated with oral progestogens, with fewer hysterectomies. Women failing to regress had a high risk of cancer diagnosis at the time of the hysterectomy.

This follow-up study provides valuable information about the long-term efficacy of LNG-IUS and oral progestogens for treating CH and ACH. The inclusion of the vast majority of eligible women and the size of this study eliminates potential selection bias. We achieved a very high percentage of follow-up (>95%) for our primary outcome of endometrial regression at 12 months and we reduced potential follow-up bias. We also measured and adjusted for a large number of potential confounding factors. The observational design, though, cannot exclude residual confounding from unmeasured variables. Despite the retrospective recruitment of women treated with oral progestogens, in cases with incomplete data for follow-up, we obtained permissions from the relevant health

authorities to arrange and perform clinical and histological follow-up for these patients ($n = 15$) and women were recalled by contacting them through their primary care clinicians. This is justified by the high relapse rate for these women that warrants long-term follow-up (Gallos et al., 2013a,b,c) and it also reduced the amount of missing data and increased our follow-up rate up to 95%. Our follow-up strategy with endometrial sampling every 6 months for the first 2 years and yearly thereafter ensured robust surveillance. Pragmatic follow-up visits were arranged on a patient-to-patient basis at variable time intervals, but the majority of women were followed up at least yearly. No ethical issues arose from this study as participation did not affect clinical care.

The efficacy of the LNG-IUS has been assessed in a few former studies, and is consistent with our findings. These studies have all reported a regression rate above 90% (Orbo et al., 2008; Varma et al., 2008). A study previously published from our center showed that the regression rate of 109 patients treated with the LNG-IUS was 92% (Varma et al., 2008). Ultimately, we found that despite a larger cohort, our results for the regression rate with the LNG-IUS were still consistent with those previously published from our center. In terms of comparing the LNG-IUS efficacy with other therapies, there is only one other observational study, which has examined the efficacy of the LNG-IUS versus oral progestogens (Orbo et al., 2008). Orbo et al. studied the regression rate after treatment with oral progestogens (54%) and with LNG-IUS (100%) (Orbo et al., 2008). This study used a different classification system to assess the degree of hyperplasia, which makes it difficult to compare their outcomes with the WHO94 classification criteria (Tavassoli, 2003). This study also used low dosages of oral progestogens (medroxyprogesterone 10 mg/day cyclical, 10 day use/cycle), which may account for the lower rates of regression observed.

We believe that the difference in regression and relapse rates for the LNG-IUS compared with oral progestogens for the treatment of EH found in our study can be explained by the mode of progestogen delivery. The progestogen concentration in the uterine mucosa when delivered through an intrauterine device and directly into the cavity is reported to exceed that of the oral treatment by several-folds (Nilsson et al., 1982). Additional issues of compliance (100% with the LNG-IUS) and adverse effects such as nausea, weight gain, headaches, thrombophlebitis and hypertension, also limit the overall efficacy of oral progestogens. The LNG-IUS is associated with higher patient satisfaction and therefore patients are more likely to continue the treatment (Lethaby et al., 2000), which may explain its better efficacy in treating EH compared with oral progestogens. In addition, the duration of the treatment appears to be an important factor for achieving disease regression and avoiding hysterectomy. We appreciate that clinicians may consider hysterectomy sooner in women who fail to show regression with oral progestogens, especially if they have completed 12 months of treatment, but with the LNG-IUS they may prefer to wait for longer. The LNG-IUS provides a standard daily dose of progestogens for 5 years, whilst the oral progestogen treatment is likely to be discontinued by clinicians following evidence of disease regression. Interestingly, the duration of treatment with oral progestogens was usually 6 months (64%) and occasionally extended up to 12 months (6%), but regression continued to occur during follow-up and in some cases, when the treatment was actually stopped. However, the regression rate survival curve in Fig. 2 is steeper for LNG-IUS than for oral progestogens from 6 months onwards, reflecting perhaps the common clinical practice of prescribing oral progestogens for 6 months. We can hypothesize that if oral

progestogens were prescribed for longer duration their survival curve may have resembled that of LNG-IUS more closely. Spontaneous regression of SH and CH, even with no treatment, has been described before (Kurman et al., 1985), and a study observed a spontaneous regression rate up to 50% during follow-up (Orbo et al., 2008). This is likely to occur in perimenopausal women as they become menopausal and cease their anovulatory cycles causing estrogen to decline. Further research should be directed in identifying prognostic factors that could help recognize such patients as well as patients who are less likely to respond to the LNG-IUS treatment. Several biomarkers have been tested for diagnostic purposes, but for predicting response to progestogens only BMI and the estrogen and progesterone receptor profile appear predictive for women treated with the LNG-IUS (Allison et al., 2008; Akesson et al., 2010; Gallos et al., 2010, 2013a,b,c).

This study has important clinical implications, as it supports the use of the LNG-IUS for CH, to avoid unnecessary hysterectomy. LNG-IUS was found to have higher regression and lower hysterectomy rates compared with the oral progestogens. These findings support a change in clinical practice where the LNG-IUS should be offered as treatment of choice and oral progestogens should be offered as an alternative. The regression and hysterectomy rates of LNG-IUS and oral progestogens for EH reported in this study can help counsel women and aid an informed therapeutic decision. This study finds that endometrial cancer is commonly diagnosed in women who fail to show regression. Consequently, we recommend that hysterectomy is at least considered if histological surveillance beyond 12 months from diagnosis fails to show regression.

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Authors' roles

I.D.G. and J.K.G. designed and executed the study. P.K., M.S., R.G. and I.D.G. analyzed the data. I.D.G. drafted the manuscript and all authors contributed to the critical discussion.

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Conflict of interest

There are no conflicts of interest to declare.

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